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Vitamin C and exercise-induced immunodepression [Letter to the Editor]

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Moreira et al. (2007) systematically reviewed the role of nutrition on exercise-induced immunodepression. Their paper has several shortcomings, however.

Moreira refers to Nieman's "J"-curve hypothesis, which proposes that moderate exercise improves the immune system and reduces the risk of upper respiratory tract infections (URI), whereas excessive physical stress impairs the immune system and increases URI risk (Nieman 1994). In a large cohort, we found that the risk of the common cold and pneumonia were not reduced with moderate physical activity, refuting the universal validity of the "J"-model (Hemilä *et al.* 2003, 2006).

Although excessive physical stress plausibly impairs the immune system, respiratory symptoms after a marathon run (Peters & Bateman 1983) do not imply viral etiology because sore throat, cough and nasal symptoms can result from several hours of exceptional ventilatory exertion. Many similar studies lack evidence that respiratory symptoms were caused by infections. Pneumonia is a well defined infection and heavy exertion is characteristic for military recruit training, and therefore increased pneumonia risk in recruits is important when considering exercise-induced immunosuppression (Hemilä 2004). For example, Navy and Marine personnel with less than 1 year of service were at 5 times higher risk of pneumonia than their peers with 4 or more years of service (Gray *et al.* 1994). Nevertheless, irrespective of the etiology of respiratory symptoms, nutrients such as vitamin C might be beneficial for marathon runners.

Moreira states that because of their comprehensive search strategy, omission of important trials seems unlikely. Yet, several important trials are missing from their review. If the biological focus is on physical stress, restriction to athletes is poorly justified. For example, military recruits also suffer from heavy physical stress and trials with them can add relevant information. Furthermore, Moreira ignored earlier meta-analyses on the same topic.

In 1996, I pooled the findings of three trials with participants under heavy acute physical stress: marathon runners (Peters *et al.* 1993), Canadian troops in winter exercises (Sabiston & Radomski 1975), and school children in a skiing camp in the Swiss Alps (Ritzel 1961). The incidence of the common cold was significantly lower in the vitamin C groups: pooled RR = 0.50 (95% CI 0.35-0.69) (Hemilä 1996). In 2004, we updated the meta-analysis by adding three newer trials, all with marathon runners (Peters *et al.* 1996; Moolla 1996; Himmelstein *et al.* 1998 [see also Himmelstein 1996]). The estimated benefit did not change, but the confidence interval became narrower: RR = 0.50 (95% CI: 0.38-0.66; P = 0.000,001) (Douglas *et al.* 2004). Moreira states that further studies are needed to provide unequivocal proof of effect by vitamin C, but in our 2004 meta-analysis we already had three additional trials with physically stressed people, all consistent with the 50% benefit (Douglas *et al.* 2004). Thus, the 50% effect calculated by Moreira is not novel and it is supported by three omitted trials.

If heavy exertion impairs the immune system, vitamin C might be beneficial for infections other than URI. Vitamin C supplementation reduced pneumonia incidence by 85% in Marine recruits (Pitt & Costrini 1979; Hemilä 2004). Furthermore, vitamin C is an antioxidant and other antioxidants might show benefits as well. In the ATBC Study, vitamin E reduced pneumonia risk in participants who exercised at leisure, RR= 0.50 (95% CI: 0.30-0.84), but had no effect on those who had heavy job activity, possibly because of adaptation to regular physical activity (Hemilä *et al.* 2006; Hemilä 2006). Vitamin E had no effect on common cold risk in physically active participants (Hemilä *et al.* 2003). Thus, these findings are partially consistent with the presumed effect of vitamin C on exercise-induced immunodepression.

Moreira calculated quality scores to the identified trials. However, because of various problems in quality scoring, the current version of the Cochrane Handbook suggests that “Reviewers should avoid the use of ‘quality scores’ and undue reliance on detailed quality assessments. It is not supported by empirical evidence, it can be time-consuming, and it is potentially misleading” (Higgins & Green 2006). Moreira calculated 8.5 points to the Himmelstein *et al.* (1998) trial, but did not mention that Himmelstein started with 52 marathon runners per study group, yet 42%(22/52) of the vitamin C group and 75%(38/52) of the placebo group dropped out during the trial. Such an extreme and significant divergence in drop-out rate (Fisher-P[2-t] = 0.003) may cause severe bias in the groups, but this possibility was not considered by Moreira. Quality scoring thus camouflaged a serious shortcoming. Nonetheless, the exclusion of the Himmelstein trial would not affect conclusions.

Proponents of evidence-based medicine argue that decisions on medical interventions should be based on clinically relevant outcomes and not on surrogates such as laboratory measurements. There are several examples where the effect on a surrogate end-point diverged from the effect on a clinically relevant outcome (Fleming & DeMets 1996). Therefore, trials which measure URI and those which measure laboratory variables of the immune system should not be presented in the same table as Moreira did, because the latter are not relevant when evaluating the clinical effects of intervention.

Finally, Moreira claims that the risks of excessive intake of vitamin C may outweigh any potential benefits. Several independent reviewers have concluded that essentially all speculations concerning the risks of vitamin C supplementation are unfounded (e.g. FNB 2000; Hemilä 2006). On the contrary, participants of a recent pharmacokinetic study were administered up to 100 grams of vitamin C intravenously over a few hours without any reported adverse effects, indicating safety of such a high single dose in healthy people (Padayatty *et al.* 2004).

In conclusion, there is strong evidence of positive effect by vitamin C on physically stressed people and there is no valid evidence that vitamin C would be harmful to ordinary people in doses of 1 to 2 grams per day. Therefore, physically active people, who consider that they suffer from colds frequently, might try vitamin C, while at the same time we hope that new trials will be carried out.

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